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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/864,685	05/24/2001	Zoltan Kiss	54938-236531	2047

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EXAMINER	
KRASS, FREDERICK F	
ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 03/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/864,685	KISS, ZOLTAN	
	Examiner	Art Unit	
	Frederick Krass	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *11-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 26-30* is/are rejected.

7)☒ Claim(s) *10* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2,3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Oath is Defective

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02. The oath or declaration is defective because it does not specify the application relied upon for priority under 35 U.S.C. 120 by a particular United States Serial Number.

Priority Claim is Defective

The claim to priority made in the oath/declaration (see above) and at the first line of the specification could not be granted, since no particular priority document is specified by United States Serial Number.

Restriction Requirement

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-10 and 26-30, drawn to compositions, classified in class 514, subclass 184 plus.

II. Claims 11-25, drawn to methods, classified in class 604, subclass 522 plus.

The inventions are distinct, each from the other because:

Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the product as claimed can be used in a materially different process of using that product, e.g. treating inflammation and other medical conditions besides cancer.

Because these inventions are distinct/unrelated for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper. Moreover, because a search of each distinct/unrelated invention would not be coextensive with the other(s), and because each invention will require its own separate patentability analysis, an examination and search of multiple inventions in a single application would constitute a serious undue burden on the examiner.

During a telephone conversation between the previous examiner (Ann Lam) and Mr. Paul Busse, attorney of record, conducted on February 3, 2003, a provisional election was made with traverse to prosecute the invention of Group I, claims 1-10 and 26-30. Affirmation of this election must be made by applicant in replying to this Office action. Claims 11-25 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9 and 26-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for apoptosis/necrosis-inducing anticancer compositions comprising a dithiocarbamate compound, zinc cation, ethacrynic acid and dimethylethanolamine, does not reasonably provide enablement for apoptosis/necrosis-inducing anticancer compositions not containing these particular agents in combination. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) the breadth of the claims.

The instant specification fails to provide guidance that would allow the skilled artisan to practice the instant invention without resorting to undue experimentation, as discussed in the subsections set forth hereinbelow.

1. The nature of the invention, state of the prior art, relative skill of those in the art, and the predictability of the art

The claimed invention relates to the treatment of cancer.

The relative skill of those in the art is generally that of a PHD candidate or PHD.

USP 5,919,816 represents a standard publication in the art and as such is directed to those having ordinary skill in the art.

USP 5,919,816 demonstrates the unpredictability of the claimed subject matter. See for example column 1, lines 35-65, which teaches that the mechanisms by which anticancer drugs work are not well-understood. See also the various case law which

supports the assertion that the art of cancer chemotherapy is unpredictable, e.g. Ex parte Timmis, 123 USPQ 581 (1959) and In re Butting 163 USPQ 689 (1969).

WO 00/61142 further demonstrates the unpredictability of the claimed subject matter, and shows that when combinations of anticancer agents are used (as is the case instantly), the upredictability of the cancer art increases. See the first two lines of the second paragraph on page one of the prior art reference, as well as the full third paragraph on the same page, for example, which clearly teach that the efficacy of combination cancer therapies must be determined in an empirical manner, with extensive and painstaking testing, and without an *a priori* expectation of success for any given combination.

The situation becomes even more tenuous when the ability of a given agent or combination of agents to induce apoptosis is invoked. It is well-known that apoptosis is extremely complicated, poorly understood, and must be determined on a case-by-case for each apoptotic mechanism involved. See USP 6,231,852 at column 2, lines 5-11, for example.

Given the above facts, it is clear that the art to which the instant invention relates involves a very high degree of unpredictability.

2. The breadth of the claims

Claims 1-9 and 26-30 are very broad and inclusive of an extremely large number of potential combinations of chemotherapeutic agents.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for preparing apoptosis/necrosis-inducing anticancer compositions, other than those containing a dithiocarbamate, zinc cation, ethacrynic acid and dimethylethanolamine, which is the only combination actually tested in the working examples. (Indeed, the experiments set forth at pages 37-39 of the instant specification appear to corroborate the unpredictability of the art, and demonstrate that each agent alone is ineffective in inducing apoptosis). Note too that the broad class of "dithiocarbonyl" compounds as recited instantly is not enabled, but rather the narrower class of "dithiocarbamate" compounds is.

4. The quantity of experimentation necessary

Applicant fails to provide guidance and information sufficient to allow the skilled artisan to ascertain which anticancer agent combinations, known or to be discovered, can reasonably be expected to be "capable of inducing apoptosis or necrosis" without resorting to undue experimentation, other than dithiocarbamate/zinc/ethacrynic acid/diemthylethanolamine. Testing would have to be conducted on many other

combinations, with no expectation of success for treatment of any particular combination other than dithiocarbamate/zinc/ethacrynic acid/diemthylethanolamine.

Obviousness Rejection

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lacreta et al ("Pharmokinetics and Bioavailability Study of Ethacrynic Acid as Modulator of Drug Resistance in Patients with Cancer", *Journal of Pharmacology and Experimental Therapeutics*, vol. 270, no. 3, pp. 1186-1191 (1994)) in view of Crescenti (USP 5,698,583).

The primary reference discloses the use of ethacrynic acid to decrease resistance to various anticancer drugs (see the abstract). It differs from the instant claim insofar as it does not specify incorporating a zinc cation.

The secondary reference teaches that zinc exerts a cell-protective function which permits anticancer agents to be used in amounts of 10 times or greater that normally used (column 4, lines 55-60). The cancer is killed by, *inter alia*, necrosis: see column 15, lines 57-38. It differs from the instant claim insofar as it does not specify the use of ethacrynic acid.

It would have been obvious to have increase the therapeutic efficacy of the treatment methods of the primary reference by increasing the amount of anticancer agent used, by using zinc cojointly therewith as a cell-protecting agent as taught by the secondary reference.

Allowable Subject Matter

Claim 10 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

The prior art does not fairly suggest, teach or disclose the specific apoptosis/necrosis-inducing combinations specified in claim 10, which are enabled for that purpose as demonstrated in the instant working examples.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frederick Krass whose telephone number is (703) 308-4335. The examiner can normally be reached on Monday, Tuesday and Thursday from 9am to 5pm, and on Friday from 11am to 7pm. The examiner is off Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel, can be reached on (703) 308-4725. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0193.

Frederick Krass
Primary Examiner
Art Unit 1614